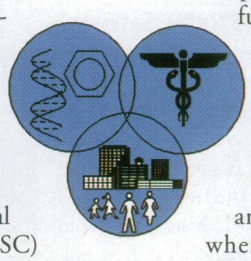
Taking the City to Heart in the Center of the City



Despite the new understanding and benefits to society provided by research centers, such institutions are frequently branded by the lay public as "ivory towers." But this criticism cannot be leveled at the Environmental Health Science Center (EHSC) for Molecular and Cellular Toxicology with Human Applications, located at Wayne State University in downtown Detroit, Michigan. The center is literally surrounded by the issues into which it delves most deeply.

Detroit's citizens are heavily hit with the consequences of pollution and poor environmental policies. For example, one out of three Detroit children under age 5 who are tested have lead poisoning (defined by CDC guidelines as 10 micrograms/deciliter). This rate is four times the national average—and only an estimated 10% of children in the area have been tested. Rates of asthma in Detroit are among the highest of affected urban areas in the country: a 1996 study published in *Pediatrics* found that, of 380 children in two Detroit schools, 14% had active, diagnosed asthma.

Raymond F. Novak, director of the Institute of Chemical Toxicology and founding director of the Wayne State University EHSC, constructed the center with the goal of stimulating high quality research using contemporary molecular and cellular approaches that would contribute to understanding the effects of real-life exposure to environmental toxicants on human health. Accordingly, the center was established with numerous programs that bring basic, clinical, and population scientists together in an effort to translate mechanistic bench science into effective preventive, treatment, and policy measures. In addition, the center employs a staff dedicated to disseminating the results of the research to the public, not only via established media conduits, but through publications, seminars, symposia, and educational science programs for local students and their teachers. "We've tried to keep our focus on environmental problems relevant to urban populations," says Novak. "We have considerable ethnic diversity in our area that allows us to investigate the susceptibility of different ethnic groups to environmental factors in disease causation. We're committed to helping the community understand the fundamentals of toxicology and use that knowledge in their daily lives."

Human Applications

Researchers of all stripes have often bemoaned the lack of contact between basic and clinical scientists, and the frequent delays that occur when sculpting innovative scientific results into a form that benefits patient treatment and outcomes. When Novak first came from Chicago's Northwestern University Medical School to Wayne State University in 1988, he saw that the molecular and cellular biological approaches that were being used nationally would be of enormous benefit to toxicology and environmental health. When the center was formed in 1993, Novak began recruiting investigators who would be able to help the field make that jump.

"We wanted to do mechanistic research that would determine how chemicals exert their effects, and take that into the realm of human populations," he says. "For instance, there's the question of how humans respond to low-level environmental exposure to chemicals over 50–70 years. While other investigators may use similar approaches, here it's the major emphasis."

The center is divided into four basic research cores and four facility cores that provide valuable material and technical support for the researchers at the center, as well as throughout the Wayne State University system and to other institutions. The center also supports programs for pilot projects, faculty enrichment, and community outreach.

Developing avenues of communication between basic and clinical researchers is the mission of Melissa Runge-Morris, a physician-scientist and director of the center's human applications core (HAC). Runge-Morris organizes biweekly HAC seminars, where researchers explain their ongoing programs and invite comments and participation from interested potential collaborators.

The HAC meetings have proven fertile ground for interdisciplinary projects. One resulting project is a collaboration between Novak, Runge-Morris, Thomas Kocarek, director of the center's cell culture facility, and Fred Miller, a professor of pathology at the Barbara Ann Karmanos Cancer Institute at Wayne State University. The group is examining the role of exposure to organochlorines, pesticides, and other chemicals in a nude mouse explant model. This model uses Ha-*ras*-transformed MCF10AT human breast epithelial cells that, when implanted subcutaneously in the mice, lead to the formation of small nodules that consist of normal ducts. "In about 10–15% of the cases, the nodule will progress through all the stages of carcinoma to fully malignant breast carcinoma," Novak says. "We want to ask how certain chemicals and doses, either potentially carcinogenic or protective, will affect the number of positive responses and the overall rate of progression to fully malignant breast carcinoma."

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are a long-recognized environmental problem, particularly in urban areas, with the Detroit metropolitan area being no exception. Several of the center investigators are engaged in research to understand the mechanisms whereby these compounds exert their toxic effects. Much of this effort is centered around the aryl hydrocarbon receptor (AhR) and the expression of its target genes. PAHs such as benzo[*a*]pyrene, as well as halogenated hydrocarbons such as dioxin, have been shown to bind the AhR with high affinity, activating it to a potent transcription factor. The activated receptor has been shown to alter the expression of a variety of genes associated with toxicant metabolism, differentiation, and cell cycle control.

Ron Hines, a professor of pharmacology and deputy director of the Wayne State University EHSC, has been studying a unique negatively acting transcription factor capable of modulating the AhR's ability to induce expression of human *CYP1A1*, the enzyme responsible for converting PAHs into carcinogens. Abnormal regulation of the *CYP1A1* gene has been linked to an increased susceptibility to lung cancer. Hines speculates that genetic defects in the gene

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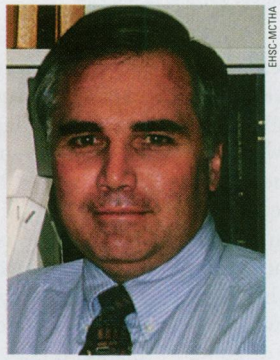
Solutions for cities. Researchers at the Wayne State EHSC work to find solutions to the urban environmental problems of Detroit and other cities.

encoding the negatively acting transcription factor might be involved in this abnormal regulation, and therefore may prove to be a powerful diagnostic tool. John Reiners, Jr., director of the cell signaling and function research core and a professor of toxicology at the Institute of Chemical Toxicology, and Cornelius Elferink, an assistant professor of toxicology at the same facility, have demonstrated that AhR function is down-regulated in cells and tissues expressing the Ha-*ras* oncogene. This finding, coupled with the expression of oncogenic *ras* genes in 30% of all human tumors, may provide a plausible basis for the observed altered regulation of AhR-responsive genes in many human tumors.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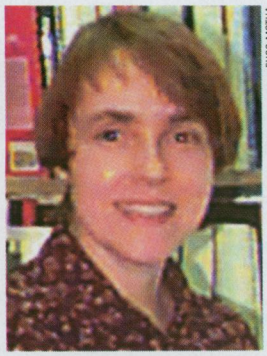
Ron Hines

New Research on Metals

Metallic toxicants such as arsenic and lead are important and ubiquitous environmental health hazards. Arsenic, for example, can be found in amounts of 1–2 parts per billion in great portions of the earth's crust. Lead is still used as a gasoline additive in many countries, which leads to its dispersal via automobile exhaust and subsequent inhalation. Lead paint poisoning, which has a variety of neurological effects, is still a significant problem in the United States, particularly for inhabitants of older, urban housing where lead paint and lead-soldered pipes are found.

Experts at the Wayne State University EHSC have joined together to try to understand the molecular biological dynamics of lead's toxicity. Modulation of the critical bone matrix protein osteocalcin by lead has been extensively described by Joel Pounds, a professor of toxicology at the Institute of Chemical Toxicology, who is now working with Lisa Elferink, an assistant professor of biological sciences at Wayne State University, to understand lead's effects on synaptic function. The link between these areas may be calcium, because lead appears to act as a surrogate for calcium, in some biological systems. This research could lead to better understanding and possibly prevention of the skeletal and neurological consequences of lead poisoning.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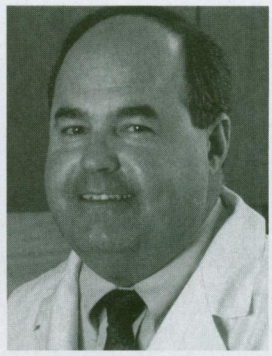
Melissa Runge-Morris

While the skeletal and neurological effects of lead have been known for some time, recently researchers have become aware of lead's possible impact on the immune system. Center investigator Michael McCabe was one of the first to demonstrate this, showing that lead interferes *in vitro* with the function of CD4+ Th1 T cells. "Our initial studies have been showing an up regulation of humoral immunity and a down regulation of cell-mediated immunity in the presence of lead," says Reiners, who is collaborating with McCabe. "These are processes that have not been attributed to lead before. The question is, are such effects relevant to humans?"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Raymond Novak

Although exposure to manganese has long been suspected to play a role in the development of Parkinson's disease, it is now thought that lead may also play a part in this disease. Epidemiology core director Christine Cole Johnson recently collaborated with EHSC members neurologist Jay Gorell, genetic epidemiologist Ben Rybicki, and biostatistician Edward Peterson, all of the Henry Ford Health System in Detroit, as well as Eugene Kortsha, an industrial hygienist and a pioneering figure in General Motors' industrial hygiene program. These investigators have looked for associations between metal exposure and Parkinson's disease among the population served by the Henry Ford Health System, who constitute about 25% of the population of the Detroit metropolitan area. Analyses of the data confirmed an association with occupational lead exposure.

This team, along with Pounds, is now working to confirm this association using other markers of lead exposure, such as K X-ray fluorescence. The technique allows researchers to estimate the difference in lead levels between cortical and trabecular bone, which they hope will allow a better approximation of exposure. The group may also look at other possible indicators of susceptibility to Parkinson's disease such as p450 variants, which are thought to regulate the metabolism of toxicants.


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Christine Johnson

Public health concern over arsenic has come to a head as the EPA reviews its standards for the metal in drinking water. Chronic exposure to arsenic causes a wide variety of health problems ranging from general fatigue and debilitation to abnormal pigmentation, hyperkeratosis, and carcinogenesis. Chronic exposure has been found in populations drinking from deep-water wells in areas of high iron ore content such as Bangladesh, West Bengal, Taiwan, and southeastern Michigan. As Chris States, director of the center's regulation of gene expression core, explains, arsenic enters the water supply when air oxidizes the pyrite in ore, forming arsenic oxygen anions. "It's estimated that there are about 350,000 people in this country who depend on water sources that are above the EPA's limit for arsenic, so it's considered a problem," States says.

Oddly enough, arsenic does not cause mutagenesis *in vitro*, so it's very difficult to determine why it causes cancer. "It does cause chromosomal instability," States says, "and research from the mid-[19]80s shows that it enhances gene amplification in some mouse cell models. So it may interfere with mitosis, but that's certainly not the whole answer."

States has assembled a team of researchers from throughout the center to study arsenic. Barry Rosen, chairman and a professor of the department of biochemistry and molecular biology in the School of Medicine at Wayne State University, has already looked at how organisms build resistance to arsenic after sublethal exposure. McCabe will look at the aspect of immunotoxicology and metals. Reiners will investigate how skin cancers arise from arsenic exposure. Pounds and States will follow up on their recent observation that transformed fibroblasts are more sensitive to arsenic than untransformed cells. "This is a collaboration designed in heaven," Reiners says. "You couldn't ask for five experimenters with more marriageable expertise."

Facility Cores

About 65% of the center's budget goes to maintaining the center's four facility cores. These facilities enable investigators to design and investigate useful research questions. As Novak points out, the expertise and availability of Ye-Shih Ho, director of the transgenic animals/gene knockout facility core, is invaluable when determining whether certain experiments will yield valuable toxicological results. Novak and Reiners also point to the cell culture facility, led by Kocarek, as an important resource for investigators.

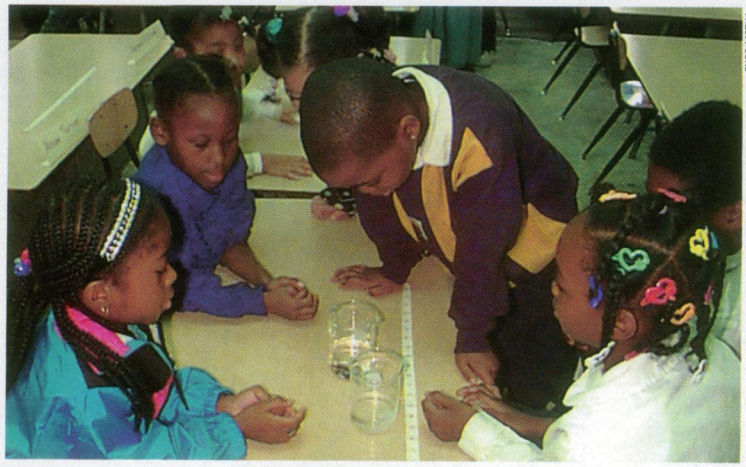
"There are large numbers of us here using the MCF10A cell lines and derivatives," says Reiners, "and whenever we place an order, the cells are ready to go. It makes for great uniformity in terms of comparing my results with those of another lab, and that's not a trivial issue; some other labs on this campus get different answers to the same questions because the experimental cell line has deviated. So it's nice to have a common source that's well monitored."

The molecular and cellular imaging and cytometric core, directed by McCabe and Kamiar Moin, also provides investigators with a variety of technologies to examine mRNA expression, protein localization, the effects of the cell cycle on gene expression and protein levels, apoptosis, and other cellular endpoints.

Outreach

Bringing the benefits of toxicology research to the surrounding community is perhaps the greatest of the center's challenges. Mary Dereski, program leader for community outreach and education, can frequently be found in local schools and science classes showing students why they should be aware of toxicants in their environment. "We'll actually do some materials lead testing in the classroom with a kit," she says, "and the kids are just fascinated. We'll bring in a painted bedpost, maybe a piece of trim from a window, things like that. There was one student who was wearing a necklace made of lead shot. Of course, it tested positive for lead. In speaking with him, it came out that he had been putting this necklace in his mouth and chewing it. By participating in this program, he was informed of the adverse effects of lead and the necessity of refraining from further ingestion of lead."

The educational program is in great demand and sought by science teachers within the metropolitan Detroit area, including the Detroit public school system, Novak says. Additional programs have been created to further entice local students into science education and, eventually, science careers. A toxicology newsletter, *The Link*, is published for teachers in the area served by the center, and there are high school and junior high science awards programs. Selected teachers and their students are also invited to the annual symposium and to research meetings at the center, where they can gain exposure to the process of science. "I think we're really reaching out to a lot of people who may have a budding interest in this area," Dereski says. "We're linking teachers and students with real scientists, and letting them know what goes on in a working research laboratory."



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Learning early. The Wayne State EHSC uses a strong outreach program to bring the breadth of its environmental knowledge to even the youngest citizens of the city.

But it's not just the citizens of Detroit who stand to benefit from the knowledge gained at the Wayne State University EHSC. The center has developed a site on the World Wide Web, located at http://www.toxicology.wayne.edu/, that is helping to communicate valuable information on environmental health and toxicology. The site includes descriptions of the center's research and facility cores and profiles of center members, and provides information on pilot projects, enrichment programs, and community outreach and education. Now, people in cities around the world can learn from the Wayne State University EHSC's research on the effects of urban environmental factors on human health.

John F. Lauerman